Eur J Vasc Endovasc Surg (2011) **42**, 731


INVITED COMMENTARY

# Comments regarding 'Correlations Between Clinical Variables and Gene-expression Profiles in Carotid Plaque Instability'

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Available online 29 September 2011

A clever and effective idea from the Karolinska Institute in Stockholm, Sweden, with collaborations between a center of Molecular Medicine and the clinical divisions of Surgery and Internal Medicine, generated this paper, capitalising on an interesting project generating a "bio-bank" (BIKE) of gene expression profiles and clinical information from 106 patients undergoing carotid endarterectomy (CE).

This paper may seem quite complex to grasp, especially for a vascular surgery readership, since it analyzes a large amount of data without any clear hypothesis testing. Therefore the reader needs to refer to the lengthy supplementary data, in order to understand the results. However, the effort of the authors' in the microarray gene analysis on more than 100 CE specimens has to be applauded.

Gene expression profiling is the measurement of the activity (the expression) of thousands of genes at once, to create a global picture of cellular and tissue functions. For this purpose, the authors utilized the DNA Microarray technology that measures the relative activity of previously identified target genes.

Therefore, the authors "chose a biased approach and limited the genes studied to 317 candidates already thought to be associated with plaque instability or healing processes in the vessel wall, and correlated the gene expression analysis to clinical parameters". The number of genes and the several clinical subgroups analyzed make statistical significant conclusions difficult to reach for any clinical translation.

Changes in the analyzed gene expression are in accordance with previously published papers showing an upregulation of genes involved in matrix degradation and inflammatory pathways in atherosclerotic plaque tissue vs control, symptomatic versus asymptomatic, statin untreated versus treated, echolucent versus ecodense plaque, MS or TIA versus AF and vice versa. From this point of view, microarray analysis is confirming the different approaches of previous studies, without giving new insights in the comprehension of plaque instability.

However there is new insight into the timing of gene expression. It is surprising that lesions removed early after symptoms (within 15 days) of plaque instability are characterized by less inflammation and proteolysis, with various smooth muscle cellmarker genes being increased and macrophage but T-cell marker genes levels decreased. Even more surprisingly, plaques removed at a later time point (more than 1 month) after symptoms, showed increased expression of genes involved in inflammatory processes and matrix degradation. This timing of "unhealthy changes in gene expression" contrasts with the clinical evidence of higher risk of cerebrovascular events in the first 2 weeks after index symptoms.

The authors' offer a sound final conclusion, that their bio-bank platform could be used in the future to explore new unknown mediators and pathways of carotid plaque instability and healing. To reach this future goal, it may be interesting to use the serial analysis of gene expression (SAGE) technique, which is a sequence-based sampling technique not based on hybridization, so that the mRNA sequences do not need to be known *a priori* and novel genes and gene variants, not yet known, can be discovered.

DOI of original article: 10.1016/j.ejvs.2011.05.023.
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1078-5884/$36 
doi:10.1016/j.ejvs.2011.06.045